Complete Summary

GUIDELINE TITLE

Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society.

BIBLIOGRAPHIC SOURCE(S)

Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, Baram TZ, Duchowny M, Hirtz D, Pellock JM, Shields WD, Shinnar S, Wyllie E, Snead OC 3rd. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004 May 25;62(10):1668-81. [68 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Infantile spasms

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Neurology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To determine the current best practice for treatment of infantile spasms in children

TARGET POPULATION

Children aged 1 month to 3 years with infantile spasms

Note: The subcommittee did not consider studies of children with Lennox-Gastaut syndrome, an epilepsy syndrome of early childhood that frequently follows infantile spasms.

INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment

1. Adrenocorticotropic hormone (ACTH)
2. Vigabatrin

The following treatments were considered but there was insufficient evidence to make recommendations concerning their use:

1. Oral corticosteroids including prednisone and prednisolone
2. Benzodiazepines including nitrazepam
3. Valproic acid
4. Pyridoxine
5. Newer antiepileptic drugs and novel therapies including zonisamide, intravenous immunoglobulin (IVIG), liposteroid, the ketogenic diet, thyrotropin-releasing hormone (TRH), and topiramate

MAJOR OUTCOMES CONSIDERED

- Complete cessation of spasms
- Resolution of hypsarrhythmia
- Normalization of electroencephalography (EEG)
- Relapse rate
- Incidence of adverse effects
- Mortality
- Nonepileptiform electroencephalograhpy (EEG)
- Normal development

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The OVID interface was used to search both MEDLINE (1966 to May 2002) and EMBASE (1980 to May 2002) databases simultaneously. The search term "spasms, infantile" retrieved a total of 2,616 references. A text word search was also used to identify other potentially relevant studies. Terms used included the following: infant: spasm, hypsarrhythmia, hypsarrhythmi, cryptogen: infant: spasm, jackknife seizure, nodding spasm, salaam seizure, spasmus nutans, symptomatic infant: spasm, west syndrome:, lightning attack, salaam attack and blitznicksalaamkrampfe, petit mal quadrette, massive myoclon: spasm, and minor motor epilepsy. The wildcard symbol ":" was used to truncate words, allowing retrieval of articles that used variations in word endings. The combined MEDLINE and EMBASE text word searches identified 1,175 articles. All search titles and abstracts were analyzed for content. English language articles on therapy, prognosis, and side effects were selected, including original and review articles. There were 159 articles chosen for detailed review.

Articles included for analysis required the following: 1) A clearly stated diagnosis of infantile spasms. 2) An electroencephalogram (EEG) demonstrating hypsarrhythmia or modified hypsarrhythmia. Hypsarrhythmia is defined as very high voltage random slow waves and spikes in all cortical areas. The spikes vary from moment to moment in duration and location. Modified hypsarrhythmia includes variations such as hypsarrhythmia with increased synchronization, asymmetrical hypsarrhythmia, hypsarrhythmia with a consistent focus of abnormal discharge, hypsarrhythmia with episodes of attenuation, and hypsarrhythmia with little sharp wave activity or spike activity. Articles using a routine EEG recording were acceptable for inclusion because very few articles used video-EEG monitoring. 3) Age of 1 month to 3 years. Infantile spasms were classified as either symptomatic or cryptogenic as defined by the International League Against Epilepsy. The symptomatic group is characterized by "previous existence of brain damage signs (psychomotor retardation, neurologic signs, radiologic signs, or other types of seizures) or by a known etiology." The symptomatic group can be further divided into prenatal, perinatal, and postnatal groups. Prenatal causes include chromosomal abnormalities, inborn errors of metabolism, neurocutaneous syndromes, cortical malformations, and intrauterine infections. Perinatal causes include hypoxic ischemic encephalopathy and birth trauma. Postnatal causes include central nervous system (CNS) trauma, infection, and intracranial hemorrhage. The smaller cryptogenic group is characterized by "a lack of previous signs of brain damage or of known etiology." Cases described as idiopathic or "doubtful" and post immunization were included in the cryptogenic group for analysis.

For the purposes of this practice parameter, the subcommittee did not consider studies of children with Lennox-Gastaut syndrome, an epilepsy syndrome of early childhood that frequently follows infantile spasms. Studies were excluded if the

patient's age was <1 or >36 months at the time of entry into the study or if an EEG was not performed to confirm the diagnosis of hypsarrhythmia or modified hypsarrhythmia. Retrospective studies were excluded if they were single case reports or case series with fewer than four infants. Studies on long-term prognosis that were uncontrolled for treatment, letters, abstracts, and unpublished data were also excluded.

NUMBER OF SOURCE DOCUMENTS

159 articles were selected for detailed review

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

American Academy of Neurology Evidence Classification Scheme for a Therapeutic Article

Class I: evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) is/are clearly defined.
b. Exclusion/inclusion criteria are clearly defined.
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a randomized control trial in a representative population that lacks one criteria of a–d.

Class III: all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: evidence from uncontrolled studies, case series, case reports, or expert opinion.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Individual committee members reviewed, abstracted, and classified the selected articles to assess the quality of evidence-based data related to study design and treatment effect. Outcome measures included short- and long-term measures. Short-term outcome measures were defined as 1) complete cessation of spasms, 2) resolution of hypsarrhythmia and, where documented, normalization of electroencephalography (EEG), and 3) relapse rate. Adverse effects and mortality were documented. In studies with a mean follow-up of >2 years, long-term outcome measures were 1) nonepileptiform EEG, 2) absence of seizures, and 3) normal development. Stringent criteria were not used in the analysis of the developmental outcome data because the results of developmental assessments were often based on clinical impression, developmental screening tools, and school placement rather than standardized, age-appropriate psychometric testing. There are very limited natural history data on infantile spasms. Thus, it is impossible to accurately quantify, but at least some children do spontaneously remit, approximately in the order of 10 to 25% according to older and uncontrolled reports. Data recorded included description of the number of patients entering and completing the trial, age at onset of spasms, age at entry into the study, sex, etiology, drug dosage, duration of therapy, co-interventions, and duration of follow-up.

A four-tiered classification scheme for diagnostic evidence recently approved by the Quality Standards Subcommittee was utilized as part of this assessment (see "Rating Scheme for the Strength of the Evidence" field). Depending on the strength of this evidence, it was decided whether specific recommendations could be made and, if so, the strength of these recommendations (see below "Rating Scheme for the Strength of the Recommendations" field). Evidence pertinent to each treatment together with the committee's evidence-based recommendations is presented.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When formulating the recommendations the guideline developers considered the magnitude of the effect (benefit or harm of therapy, accuracy of tests, yield of studies) and the relative value of various outcomes. Under most circumstances, there is a direct link between the level of evidence used to formulate conclusions and the strength of the recommendation. This linkage is illustrated in Appendix 9 of the 2004 AAN Guideline Process Manual (see Companion Documents field). Thus, an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation; a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation; a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation. In those circumstances where the evidence indicates that the intervention is not effective or useful, wording was modified. For example, if multiple adequately powered class I studies demonstrated that an intervention is not effective, the recommendation read, "should not be done."

There are important exceptions to the rule of having a direct linkage between the level of evidence and the strength of recommendations. Some situations where it may be necessary to break this linkage are listed below:

- A statistically significant but marginally important benefit of the intervention is observed
- The intervention is exorbitantly costly
- Superior and established alternative interventions are available
- There are competing outcomes (both beneficial and harmful) that cannot be reconciled

Under such circumstances the guideline developers may have downgraded the level of the recommendation.

Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

American Academy of Neurology System for Translation of Evidence to Recommendations

Rating of Recommendation

A = established as effective, ineffective, or harmful for the given condition in the specified population.

B = probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population.

C = possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.

U = data inadequate or conflicting. Given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Guidelines were approved by the Quality Standards Subcommittee (QSS) on July 26, 2003, the American Academy of Neurology (AAN) Practice Committee on November 16, 2003, and the AAN Board of Directors in January 2004.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Effectiveness of Adrenocorticotropic Hormone (ACTH) and Oral Corticosteroids in the Treatment of Infantile Spasms

1. ACTH is probably effective for the short-term treatment of infantile spasms and in resolution of hypsarrhythmia (level B).
2. There is insufficient evidence to recommend the optimum dosage and duration of treatment with ACTH for the treatment of infantile spasms (level U).
3. There is insufficient evidence that oral corticosteroids are effective in the treatment of infantile spasms (level U).

Effectiveness of Vigabatrin in the Treatment of Infantile Spasms

1. Vigabatrin is possibly effective for the short-term treatment of infantile spasms (level C, class III and IV evidence).
2. Vigabatrin is also possibly effective for the short-term treatment of infantile spasms in the majority of children with tuberous sclerosis (level C, class III and IV evidence).
3. Serious concerns about retinal toxicity in adults suggest that serial ophthalmologic screening is required in patients on vigabatrin. However, data are insufficient to make recommendations regarding the frequency or type of screening that would be of value in reducing the prevalence of this complication in children (level U, class IV studies).

Other Agents Evaluated for the Treatment of Infantile Spasms

1. There is insufficient evidence to recommend other treatments (valproic acid, benzodiazepines, pyridoxine, newer antiepileptic drugs, or other or novel therapies) for the treatment of infantile spasms (level U, class III and IV evidence).

Long-term Outcome

1. The data are insufficient to make any recommendations regarding the use of ACTH, corticosteroids, vigabatrin, valproic acid, and pyridoxine to improve the long-term outcomes (seizure freedom and normal development) of children with infantile spasms (level U, class III and IV evidence).
2. The data are insufficient to conclude that early initiation of treatment should be used to improve the long-term outcome of children with infantile spasms (level U, class III and IV evidence).

Definitions:

Rating of Recommendation

A = established as effective, ineffective, or harmful for the given condition in the specified population.

B = probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population.

C = possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.

U = data inadequate or conflicting. Given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

American Academy of Neurology Evidence Classification Scheme for a Therapeutic Article

Class I: evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) is/are clearly defined.
b. Exclusion/inclusion criteria are clearly defined.
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a randomized control trial in a representative population that lacks one criteria of a–d.

Class III: all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: evidence from uncontrolled studies, case series, case reports, or expert opinion.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment of infantile spasms

POTENTIAL HARMS

- Adverse effects of the various treatments
- Serious concerns about retinal toxicity suggest that serial ophthalmologic screening is required in patients on vigabatrin.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, Baram TZ, Duchowny M, Hirtz D, Pellock JM, Shields WD, Shinnar S, Wyllie E, Snead OC 3rd. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004 May 25;62(10):1668-81. [68 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 May 25

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee of the American Academy of Neurology

Practice Committee of the Child Neurology Society

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

American Academy of Neurology (AAN) Quality Standards Subcommittee Members: Gary Franklin, MD, MPH (co-chair); Gary Gronseth, MD (co-chair); Charles E. Argoff, MD; Stephen Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD; Michael Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; Samuel Wiebe, MD; William J. Weiner, MD; Catherine Zahn, MD (ex-officio)

Child Neurology Society Practice Committee Members: Carmela Tardo, MD (chair); Bruce Cohen, MD (vice-chair); Elias Chalhub, MD; Roy Elterman, MD; Murray Engel, MD; Bhuwan Garg, MD; Brian Grabert, MD; Annette Grefe, MD; Michael Goldstein, MD; David Griesemer, MD; Betty Koo, MD; Edward Kovnar, MD; Leslie Ann Morrison, MD; Colette Parker, MD; Ben Renfroe, MD; Michael Shevell, MD; Shlomo Shinnar, MD; Gerald Silverboard, MD; Russell Snyder, MD; Dean Timmons, MD; Greg Yim, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Mackay has received honoraria from GlaxoSmithKline, and Janssen Cilag. Dr. Mackay has no equity, stock, or any other ownership interests in these companies. Dr. Pellock has received grants/research support in excess of $10,000 and is a paid consultant for Abbott Laboratories, Aventis, Carter Wallace (MedPointe), Elan Pharmaceuticals, GlaxoSmithKline, Ortho McNeil/Johnson & Johnson, and UCB Pharmaceuticals. Dr. Shinnar has received grants/ research support from Abbott Laboratories, Elan Pharmaceuticals, and Xcel Pharmaceuticals. He is a paid consultant for Abbott Laboratories, Cephalon, Inc., Elan Pharmaceuticals, Ovation, Pfizer Laboratories, and Xcel Pharmaceuticals. He also has received honoraria from Abbott Laboratories, Cephalon, Inc., Elan Pharmaceuticals, Pfizer Inc., the R.W. Johnson Pharmaceutical Research Institute, UCB Pharmaceuticals, Inc., and Xcel Pharmaceuticals. Dr. Shinnar has no equity, stock, or any other ownership interest in any of these companies. Dr. Shields participated in a study of vigabatrin that was partially supported by an unrestricted grant from Aventis.

ENDORSER(S)

American Epilepsy Society - Disease Specific Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Practice parameter: Medical treatment of infantile spasms. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2. p. Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site.
- Slide presentation: practice parameter: medical treatment of infantile spasms. St. Paul (MN): American Academy of Neurology. 2004. Available in Power Point from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the AAN Web site.
- Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p. Electronic copies available in Portable Document Format (PDF) from the AAN Web site.

PATIENT RESOURCES

The following is available:

Medical treatment of infantile spasms. AAN guideline summary for parents and caregivers. St. Paul (MN): American Academy of Neurology (AAN). 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

NGC STATUS

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004.

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